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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,645	04/13/2006	Masahiko Hagihara	06262/HG	4638

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EXAMINER	
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ART UNIT	PAPER NUMBER
1626	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,645	HAGIHARA ET AL.	
	Examiner	Art Unit	
	Susannah Chung	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/11/08, 7/17/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-10 are pending in the instant application.

Priority

This application is a 371 of PCT/JP04/15663, filed 10/15/2004.

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) by application nos. 2003-354917 and 2004-270561 filed in the Japanese Patent Office on 10/15/03 and 8/20/04, which papers have been placed of record in the file. The application names an inventor or inventors named in the prior application.

Information Disclosure Statement

The information disclosure statement (IDS), filed on 7/17/06 and 4/11/08 have been considered. Please refer to Applicant's copy of the 1449 submitted herewith.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims, for the reasons describe below.

As stated in MPEP 2164.01(a), "there are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

The factors to be considered when determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, were described in In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) as:

1. the nature of the invention;
2. the breadth of the claims;
3. the state of the prior art;
4. the relative skill of those in the art;
5. the predictability or unpredictability of the art;
6. the amount of direction or guidance presented [by the inventor];
7. the presence or absence of working examples; and
8. the quantity of experimentation necessary [to make and/or use the invention].

The eight Wands factors are applied to Claims 9-10 of the present invention below:

(1) The Nature of the Invention

Claims 9-10 are directed to

9. A Rho kinase inhibitor comprising the compound according to any of claims 1 to 7 or a salt thereof as an active ingredient.

10. A therapeutic agent for glaucoma comprising the compound according to any of claims 1 to 7 or a salt thereof as an active ingredient.

(2) The Breadth of the claims

Claims 9-10 will be give its broadest reasonable interpretation. The applicable rule for interpreting the claims is that "each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." See MPEP 2163(II)(1), citing In re Morris, 127 F.3d 1048, 1053-1054; 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). In view of this rule, Claims 9-10 which is directed to all Rho kinase inhibition and therapy of glaucoma will be interpreted to encompass a broad class of disorders and will be interpreted to treat and prevent those disorders, regardless of whether it is a primary or secondary method of use.

(3) The state of the prior art

The state of the pharmaceutical art in general involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat or prevent diseases related to Rho kinase inhibition).

The state of the art at the time of this application is that the etiology and treatment of Rho kinase inhibition is not well understood. Rho, a low-molecule GTP-binding protein, is activated by signals from various cell membrane receptors. It has been linked to every disorder from cancer to hypertenstion to AIDS. The mechanism of Rho kinase inhibition is not well understood.

The instant compound of formula (I) and a similar class of compounds has been shown to have some pharmacological properties. However, the specific mechanism by which the instantly claimed indazole compounds can affect various cell lines is unknown and is not disclosed in the prior art. The state of the art appears to be that more research needs to be conducted.

(4) The relative skill of those in the art

The level of skill in the art (pharmaceutical chemists, physicians) would be high.

(5) The predictability or unpredictability of the art

It is noted that the pharmaceutical art generally is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement varies inversely with the degree of unpredictability in the factors involved. In re Fisher, 427 F.2d 833, 839. Therefore, the more unpredictable an area, the more specific enablement is needed in order to satisfy the statute. Added to the unpredictability of the art itself is the question whether a showing of some pharmacological activity could reliably and predictably applied to the treatment of all types of Rho kinase inhibition. There is no absolute predictability, even in view of the high level of skill in the art.

(6) The amount of direction or guidance presented (by the inventor)

The specification in the present invention discloses that the instantly claimed compounds inhibited activity to Rho kinase (see specification pages 247-248), but does not provide any biological data such as in vivo, in vitro, population data, cell lines used or any other test to support the assertion that it can inhibition Rho kinase. In addition, the instant specification does not provide data to support the use of the instantly claimed compounds to treat any disorder.

(7) The presence or absence of working examples

The specification states that the instantly claimed compounds can inhibit Rho, but does not provide any working examples of the mechanism of action.

(8) The quantity of experimentation necessary (to make and/or use the invention)

Given the absence of direction or guidance (or working examples) in the specification for the role of the instantly claimed compounds in the inhibition of Rho or treatment of any disorder such as glaucoma, it would cause a skilled artisan an undue amount of experimentation to practice this invention to determine which patients with which diseases would benefit from which of the many claimed compounds within the scope of the invention with a reasonable expectation of success.

The instant breadth of the claim(s) is broader than the disclosure, specifically, the instant claim is directed to the inhibition of Rho kinase and the use of the compound as an agent in glaucoma, which reads on the treatment and prevention of glaucoma and a multitude of other diseases in general, but the specification, prior art or instant disclosure does not provide support for this.

Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification although enabling for a "pharmaceutical salt" of formula (I) (see specification page 27, line 5), it is not enabled for a process for preparing all salt forms of formula (I) without limitation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

(1) The Nature of the Invention

The nature of the invention is a process of making a metal complex.

(2) The Breadth of the claims

The breadth of independent Claims 1-10 encompasses all salt forms of formula (I), wherein there is no limitation on the kind of salt form. The applicable rule for interpreting the claims is that "each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." See MPEP 2163(II)(1), citing In re Morris, 127 F.3d 1048, 1053-1054; 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). In view of this rule, "salt" can be interpreted to mean any type of crystalline form from purified to unpurified.

(3) The state of the prior art

Salt forms used as pharmaceutical agents are generally known as a "pharmaceutically acceptable salt." This conveys a specific type of salt form that has a certain level of purity and has a certain level of solubility.

(4) The relative skill of those in the art

The level of skill in the art (pharmaceutical chemists, physicians) would be high.

(5) The predictability or unpredictability of the art

The salt form claimed in the instant application, where it is open ended is not predictable because one of ordinary skill in the art would not know the type of salt form being used, level of purity of the salt or any other characteristic of the salt form.

(6) The amount of direction or guidance presented (by the inventor)

The specification in the present invention discloses on page 27, starting line 5 that "salt" means "a pharmaceutically acceptable salt." This term is much clearer and is enabled.

(7) The presence or absence of working examples

The specification has no working examples of where the salt is anything other than a pharmaceutically acceptable salt.

(8) The quantity of experimentation necessary (to make and/or use the invention)

Given the absence of direction or guidance (or working examples) in the specification for any of the extremely large number of forms that would be encompassed by the term "salt," it would cause a skilled artisan an undue amount of experimentation to determine what comprises the salt form. Therefore, to overcome this rejection, amending the term "salt" to what is provided in the enabling disclosure, i.e. "pharmaceutically acceptable salt" will overcome this rejection.

Claim Rejections - 35 USC § 103

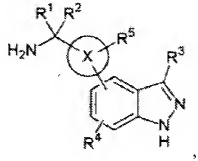
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

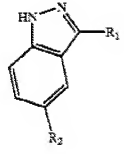
The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

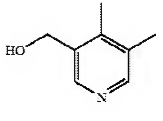
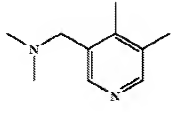
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

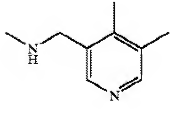
Claims 1-10 are rejected under 35 U.S.C. 103(a) as being anticipated by Reich et al., US PG Pub 2002/0161022A1, filed 10/31/02, now US Pat No 6,555,539B2 (`539 Pat).

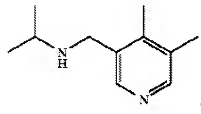
Applicants claims relate to compound of Formula (I),  , in claim 1.

Determination of the scope and content of the prior art (MPEP § 2141.01)

Reich teaches generic compounds of formula (I),  in claim 1, (`539 Pat Column 194, approx. lines 5-15), wherein R2 is a substituted aryl or heteoraryl, more specifically R2 is a substittued pyridine or phenyl group, as can be seen by the following species for R2:

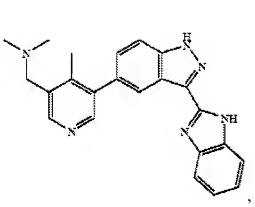
  (See claim 25, col. 227, app. lines 1-8),

 (see claim 25, column 227, approx. lines 9-13), and

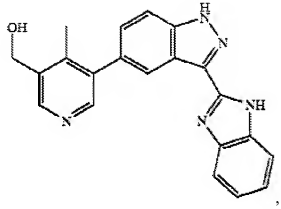


(see claim 25, column 227, approx. lines 14-18).

Reich teaches the following species of the generic compound of formula (I),



,



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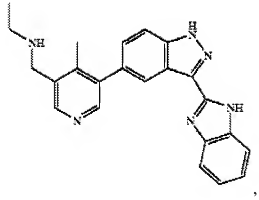

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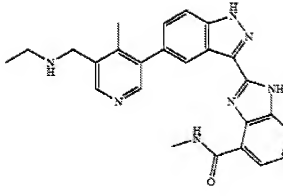

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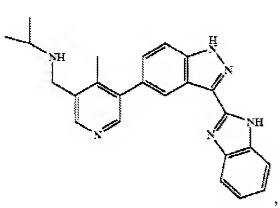
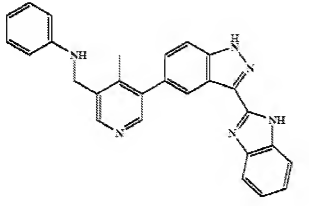


, and



(See `539 Pat, Claim 22, Columns 216 – 220.)

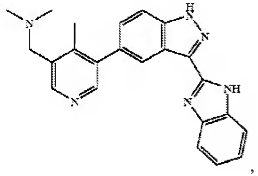
Ascertainment of the difference between the prior art and the claims (MPEP § 2141.02)

The difference between the prior art of Reich and the instant claims is the R2 variable of the `539 Pat compound. The R2 variable of the instant application is always a phenyl or pyridine moiety substituted with –CH2-NH2. The `539 Pat teaches phenyl and pyridine species for example that are substituted with –CH2-NH(alkyl) or –CH2-NH(aryl) or –CH2-OH.

Finding of prima facie obviousness – rationale and motivation (MPEP § 2142-2413)

However, in the absence of showing unobvious results, it would have been obvious to one of ordinary skill in the art at the time of the invention when faced with Reich to make the instantly claimed derivatives of a known product. The instantly claimed compounds and prior art compounds are isomers, homologues, bioisosteres, or make well known substitutions such as hydrogen for methyl of the prior art compounds.

For example, the difference between the prior art species



, found in the `539 Patent, claim 22, column 216, approx. lines 55-65, and the instantly claimed compound is that the instant claims substitute hydrogen for methyl, i.e. $N(CH_3)_2$ for NH_2. Hydrogen and methyl are deemed obvious variants. In re Wood, 199 USPQ 137.

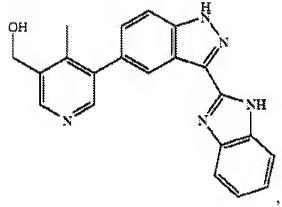
The difference between the other prior art species shown above and the instant claims is that they could be position isomers or homologs of one another. Compounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH2- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. In re Wilder, 563 F.2d 457, 195 USPQ 426 (CCPA 1977). See MPEP 2144.09(II).

Prior art structures do not have to be true homologs or isomers to render structurally similar compounds prima facie obvious. In re Payne, 606 F.2d 303, 203 USPQ 245 (CCPA 1979) (Claimed and prior art compounds were both directed to heterocyclic carbamoyloximino compounds having pesticidal activity. The only structural difference between the claimed and prior art compounds was that the ring structures of the claimed compounds had two carbon atoms between two sulfur atoms whereas the prior art ring structures had either one or three

carbon atoms between two sulfur atoms. The court held that although the prior art compounds were not true homologs or isomers of the claimed compounds, the similarity between the chemical structures and properties is sufficiently close that one of ordinary skill in the art would have been motivated to make the claimed compounds in searching for new pesticides.). See MPEP 2144.09 (III).

In addition, the instantly claimed compounds are bioisosteres of compounds are well known in the art. See Patani et al., Chem Rev, 1996, Vol. 96 (8), especially page 3147. Patani teaches that there are traditional and nontraditional bioisosteres.

For example, the difference between the prior art species



, found in claim 22, column 216, approx lines 45-50, and the instant claims is that the instant claims substitute NH2 for OH, which is a well known bioisostere (See Patini et al, page 3150, section 2, interchange of hydroxyl and amino groups.

Guided by the teaching of Reich one skilled in the art would be able to make similar compounds by substituting various well known moieties off the more complex indazole core. The motivation to optimize the compounds of Reich would be to prepare similar compounds that are pharmacologically active compounds that can be used as a pharmaceutical agent in a wide range of therapeutic areas.

The instant obviousness rejection is based on the close structural similarity of the instantly claimed compounds to the prior art compounds and the common utility shared among the compounds. There is an expectation among those of ordinary skill in the art that similar structural compounds will have similar properties and that modification of a known structure is mere experimentation within the means of a skilled artisan. See MPEP 2144.09(I). Therefore, claims 1-10 are rejected as obvious over the prior art.

Claim Objections

Claims 5, 6, 8, 9, and 10 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim shall refer to such other claims in the alternative only and a multiple dependent claim shall not serve as a basis for any other multiple dependent claim. See MPEP § 608.01(n). Appropriate correction is required.

Claims 9 and 10 are objected to under 37 CFR 1.75 as being a substantial duplicates of claims 1-7. Claim 9 is drawn to a Rho kinase inhibitor of any one of claims 1-7, which is an intended use of the compounds of claims 1-7. Claim 10 is drawn to a therapeutic agent of any one of claims 1-7 and further recites the intended use of the compounds. However, intended use is not a limitation of a compound. *In re Hack*, 114 PQ 161 (CCPA 1957). When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susannah Chung, Esq. whose telephone number is (571) 272-6098. The examiner can normally be reached on M-F, 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Susannah Chung
July 22, 2008

/Joseph K McKane/
Supervisory Patent Examiner, Art Unit 1626